## REMARKS

In the Final Office Action dated August 9, 2007, claims 1-18 and 79-137 are pending, of which claims 4-8, 17, 79-80, 89-99, 101, 107, 111-115, 121-123 and 126-137 are withdrawn from consideration. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, and 124-125 are under examination and are rejected.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

***35 U.S.C. §112, First Paragraph- Written Description***

Claims 1-3, 9-16, 18, 103-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Specifically, the Examiner contends that the specification does not provide written description support for any molecule in complex with "a GPI moiety", except for an antigenic peptide or protein. The Examiner does acknowledge that the specification discloses on page 20, at lines 29-31, that the term "GPI complex" is a reference to a GPI moiety coupled to any other molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein. However, the Examiner states that adequate written description requires more than a mere statement that it is part of the invention along with a recitation of a function such as inducing Th cells.

Applicants respectfully disagree with the Examiner. The GPI molecule is presently characterized in the claims as comprising a core glycan (i.e., the GPI molecule can include additional constituents). The specification clearly describes that a GPI molecule can be further

substituted with sugars, phosphates and ethanolamine groups and the GPI fatty acid moieties can also be substituted or modified. See, e.g., page 2, top paragraph. Therefore, Applicants respectfully submit that the specification has adequately described a representative number of species within the genus of a GPI "complex", in a manner consistent with the written description requirement.

In the last paragraph on page 3 of the Action, the Examiner also states that a definition by function does not suffice to describe the genus, because the function is merely an indication of what the property the "peptide" has, rather than what it is. The Examiner seems to be objecting to a GPI complex to the extent that the complex comprises a peptide. The Examiner's language in this paragraph seems to be contradictory to the preceding paragraphs of the Action, where the Examiner acknowledges that the specification has provided an adequate written description in relation to GPI complexes comprising an antigenic peptide or protein. Applicants therefore assume that the Examiner meant to reference carbohydrate or other non-peptide agents which might be complexed with the GPI in this paragraph of the Action. Nevertheless, as submitted above, the specification provides adequate discussion in relation to the structure of a GPI molecule and the various substitutions which can be made to that molecule. Therefore, contrary to the Examiner's allegation that the specification only describes what a complex does, rather than what a complex is, Applicants respectfully submit that the specification does describe a sufficient number of species within the genus of a GPI "complex" in a manner that fully satisfies the written description requirement.

Accordingly, the written description rejection under 35 U.S.C. § 112, first paragraph is overcome and withdrawal thereof is respectfully requested.

***35 U.S.C. §112, First Paragraph- Enablement***

Claims 1-3, 9-16, 18, 103-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. §112, first paragraph, for lacking enablement.

One aspect of the rejection is directed to the use of a "GPI complex" in the claimed methods. The Examiner contends that the specification does not provide enabling support for any molecule in complex with "a GPI moiety", except for an antigenic peptide or protein.

As submitted above, a GPI molecule includes a core glycan, i.e., it can include additional constituents. Further, a GPI molecule can be further substituted with sugars, phosphates and ethanolamine groups and the lipid moiety can also be substituted or modified, as described in the specification (page 2, top paragraph). Applicants further respectfully submit that those skilled in the art would be able to readily make a GPI complex as defined in the present application. The subject GPI molecule carries a free primary amine within the ethanolamine head group which easily undergoes amino-carboxy coupling to any manner of agent. These agents can be either proteins or carbohydrates. The coupling chemistry is straightforward and well within the ken of those skilled in the art. Therefore, Applicants respectfully submit that it would not take undue experimentation to generate and use a GPI complex as defined in the present application.

The Examiner has also maintained the aspect of the enablement rejection regarding treatment or prophylaxis of *any* disease condition, in *any* mammal. In particular, the Examiner has noted in the second paragraph on page 5 of the Action that the specification does not disclose any working examples of the treatment or prophylaxis of a disease condition *in vivo*.

In the first instance, Applicants respectfully submit that it is not necessary to submit clinical data in order to satisfy the enablement requirement. Data obtained from *in vitro* analysis or animal models may be sufficient. Although the Examiner asserts that Carvalho et al. (2002)

teach that mice are not good models for the study of malaria, Applicants dispute this assertion based on the previous submissions. Specifically, Applicants previously submitted that the *Plasmodium berghei* malaria infection of mice and rats is well recognized by a weight of scientific opinion to model the most important features of human malarial pathogenesis, and is used by many laboratories to provide a scientific basis and well accepted model for interventions against life threatening disease in humans. Applicants provided in the Response dated May 16, 2007, several scientific publications in support of the value of the murine malaria model: Schofield L. and Grau GE. (*Nat. Rev. Immunol. 5*: 722-735, 2005); Evans, K.J. et al. (*Blood* 107: 1192-1199, 2005); Barnell J. (*Blood* 1007: 854, 2006); and Lou et al. (*Clinical Microbiology Reviews* 14: 810, 2001). It is respectfully submitted that to those skilled in the art, the ability of GPI molecules to induce T-cell mediated immunity in *P. berghei*-infected mice, as shown in the present application, can be extrapolated to treating relevant diseases in other animals, including human. Still further, Applicants note that Carvalho et al. merely queried whether or not the use of a mouse model may be a problem. The authors did not allege that the mechanism of immunity acting in mice is in fact so different to the human that these murine models become irrelevant. Moreover, the murine models continue to be used worldwide for the study of malaria and, accordingly, Applicants respectfully submit that the position being put forward by Carvalho et al. is not reflective of the current state of the relevant art.

Moreover, Applicants also previously submitted that GPIs have been shown to activate NK-T cells (Schofield et al., *Science* 283: 225-229, 1999); and these same T cells have been further demonstrated to protect again malaria (Hansen et al., *Immunity* 18: 391-402, 2003). The Examiner has responded by stating that Hansen et al. (2003) teach that NK-T cells are correlated with *partial protection* against cerebral malaria in a mouse model or delay in disease

onset, but *not* in *prevention* of disease. The Examiner refers to the statement in Hansen et al., which, according to the Examiner, suggests that prevention of malaria was a still just a possibility in 2003.

Initially, Applicants note that the Examiner is now relying on the observations made by Hansen et al. using a mouse model, even though the Examiner has disputed the relevance of results achieved using a mouse model earlier in the Action. In any event, Applicants maintain that the mouse model is a good and well-recognized model for studying malaria and that the results of Hansen et al. provide further support for the claimed subject matter. In particular, Hansen et al. (2003) clearly demonstrate some degree of protection against cerebral malaria, which is also acknowledged by the Examiner. Hansen et al. disclose, *inter alia*, that when the CD1/NKT cell pathway is knocked out, the animals develop cerebral malaria. Accordingly, the CD1/NKT pathway protects against cerebral malaria in the preclinical model. Further, the data showed that the mice did not develop the disease; in other words, they were "protected" by virtue of the disease having been "prevented". Moreover, as defined in the specification, on pages 44-45, the term "treatment" and the term "prophylaxis" do not necessarily mean that a subject will not eventually contract a disease; in other words, the terms do not necessarily mean a *complete* prevention of the occurrence of the disease or full recovery, but there may occur amelioration of the symptoms of the disease condition. Therefore, Applicants maintain that Hansen et al. (2003) fully support the notion that the claimed methods are enabled.

The Examiner further argues, in the bottom paragraph on page 6 of the Action, that the specification does not disclose the ability of purified GPI molecules to induce T cell mediated immunity in *P. berghei* infected mice, nor does the specification disclose administering purified GPI molecules to treat or prevent malaria or any other disease or condition.

Applicants respectfully submit that the Examiner has not considered all supporting evidence as a whole in evaluating the enablement of the claims. As discussed above, GPIs have been shown to activate NK-T cells (Schofield et al., *Science* 283: 225-229, 1999), and these same T cells have been further demonstrated to protect again malaria (Hansen et al., *Immunity* 18: 391-402, 2003). Applicants respectfully submit that because these T cells are invariant and only recognize one dominant antigen (unlike conventional T cells, these T cells do not vary their T cell receptor repertoire), those skilled in the art would deduce, based on the present teaching, that expanding these T cells by exposure to purified GPI would provide protection against malaria.

In view of the foregoing, Applicants respectfully submit that the present specification provides sufficient guidance for those skilled in the art to practice the methods as presently claimed without undue experimentation. As such, Applicants respectfully submit that the enablement rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

***35 U.S.C. §102(b)***

Claims 1-3, 9-16, 18, 81-88, 100 and 102 remain rejected under 35 U.S.C. §102(b), as anticipated by Schofield et al. (*J. Exp. Med.* 177:145-153, 1993) (hereinafter "Schofield (1993)"), as allegedly evidenced by Nagata et al. (*Eur. J. Immunol.* 1993 23:1193-1196) and several other references.

The Examiner contends that Schofield (1993) teaches administration of GPI, which would inherently result in GPI binding to CD1 and activation of Th cells. Additionally, the Examiner contends that the GPIs taught by Schofield (1993) inherently have the core structure recited in the instant claims, as evidenced by the cited evidentiary references.

Applicants previously argued that the administration of GPI molecules in the Schofield (1993) reference caused the death of the host by activating macrophages which produced TNF. Further, in Schofield (1993), prior to administration of these GPI molecules, the mice were subjected to intraperitoneal administration of thioglycollate in order to elicit a dominant macrophage population. The Examiner has responded by stating that Schofield et al. (1993) teach administration of GPI by itself, which did not cause death and therefore meets the limitation of the claims.

Applicants respectfully submit that the distinctions between the claimed methods and Schofield (1993) are not just the death of mice. The protocols of Schofield (1993) are entirely different from the methods presently claimed. Schofield (1993) discloses a very specific bioassay which involves intraperitoneal administration of thioglycollaste *followed by* the intraperitoneal administration of GPI together with degalactosamine. This prior art method achieves the hyperactivation of macrophages in the peritoneal cavity. As disclosed by Schofield (1993), the hyperactivation of macrophages which is designed to be induced by this assay causes host death. It is therefore clear that the prior art method does not induce host protection, which is the outcome of the claimed invention. Moreover, in inducing an environment which is immunologically skewed to the generation of abnormal numbers of macrophages, one skews the entire immune state to a non-physiological point and one therefore cannot assume that in such an abnormal situation that one would inherently also induce T helper cell activation.

Further, Applicants respectfully submit that the bioactivity which is described in Schofield (1993) resulted from the association of GPI with TLR4 (a macrophage receptor) and *not* CD1. While the Examiner correctly notes that GPI was also administered on its own in Schofield (1993), very little response was obtained from such administration, and it was for this

reason that the extreme step was taken of coadministering GPI with degalactosamine to obtain a toxic endpoint. Moreover, since the administration of a GPI by itself, although not causing death, was also not effective, the Examiner has not established a *prima facie* case that Schofield (1993) necessarily discloses each and every element of the claimed invention, including the requirement that the GPI complex interacts and forms an association with CD1, resulting in the activation of helper T cells.

Applicants respectfully submit that there is nothing in the prior art which focuses on the activation of T cells by GPI. The Examiner apparently argues that this may have inherently occurred when GPI was administered to mice in Schofield (1993). As discussed above, in in Schofield (1993), where GPI was administered alone *there was very little response obtained* and where GPI was co-administered with other molecules, there was induced an extremely skewed immunological response where the macrophages of the peritoneal cavity were hyperactivated. It is unreasonable for the Examiner to make the assumption that in such an environment disclosed by Schofield (1993), one would expect that normal T cell induction pathways would continue to function. Because GPI was actually bound by the TLR4 receptor of the macrophages, and the macrophages were in abnormally high concentrations in the peritoneal cavity, it was likely that there would not even have been a sufficient amount of antigen to drain Peyer's Patches or other relevant lymphoid areas in order to enable stimulation of T cells to occur.

Accordingly, Applicants respectfully submit that the Examiner has not adequately established that Schofield (1993) necessarily discloses each and every element of the claimed invention, including the element that the GPI complex interacts and forms an association with CD1, resulting in the activation of helper T cells. Therefore, reconsideration and withdrawal of the § 102(b) rejection based on Schofield (1993) are respectfully requested.

***35 U.S.C. §103***

The Examiner has maintained the rejection of all pending claims under 35 U.S.C. §103(a) as allegedly obvious based on WO99/52547 and various secondary references. The Examiner has also maintained the rejection of all pending claims under 35 U.S.C. §103(a) as obvious over WO99/12562 in view of Gerold et al. (*J. Biol. Chem.* 1994, 269(4): 2597-2606) and Gerold et al. (*Mol. Biochem. Parasit.* 1996, 75: 131-143), or in view of Schofield (1993).

As a new ground of rejection, the Examiner has rejected claims 1-3, 9-12, 14-16, 18, 81-87, 100 and 102 under 35 U.S.C. §103(a) as obvious over WO96/34105 in view of Gerold et al. (1996), Gerold et al. (1994) and Joyce et al. (*Science* 279: 1541-1543, 1998).

***WO99/52547, WO99/12562***

The Examiner has admitted that the primary references, WO99/52547 and WO99/12562, do not teach the specific GPI species recited in the present claims. However, the Examiner contends that the recited GPI species are not entitled to the priority date of AU PP 6758 (October 27, 1998), and are only entitled to the filing date of the PCT application (October 27, 1999), which is after the publication of the cited primary references.

Applicants reassert that the subject matter allegedly taught in WO99/52547 and WO99/12562, which is relied upon by the Examine in raising the obviousness rejections, is found in the applicant's priority document, AU PP 6758, filed before the publication of WO99/52547 and WO99/12562. Therefore, Applicants have *effectively antedated* WO99/52547 and WO99/12562 and therefore have disqualified these documents as prior art. Applicants' position is well supported by the legal principal established in In re Stemple, 241 F2d 755, 760 (CCPA 1957), that a reference is valid only for what it discloses, and if Applicants establish priority with

respect to such disclosure, the reference is of no effect at all. In other words, it is not necessary for Applicants' priority document to disclose all the subject matter as presently claimed in order to *effectively antedate* the primary references; the priority document only needs to disclose as much as the primary references. The Examiner's rejection is therefore inconsistent with the legal principal established in In re Stemple and no explanation is provided in the Action to address this inconsistency.

Accordingly, it is respectfully submitted that the §103 rejections based on WO 99/52547 and WO99/12562 as primary references are overcome. Withdrawal of the rejections is respectfully requested.

***WO96/34105***

With regard to the Examiner's new rejection based on WO96/34105, this reference merely teaches production of antibodies in a mammalian host by administering a complex of GPI-antigen, such as a parasite polypeptide. The Examiner is making the assumption that this disclosure also teaches the activation of T helper cell. However, as is commonly known to immunologists, although T helper cells are often required for B cell responsiveness to a protein antigen, T-independent antibody responses commonly occur to microbial agents such as bacterial polysaccharides. Accordingly, one cannot make the assumption that the GPI molecule which has been attached to the protein in this prior art document is in fact functioning via a T cell dependent mechanism. In fact, it is generally understood that there are certain properties of some bacterial polysaccharides, polymeric proteins and lipid polysaccharides which enable stimulation of naive B cells in the absence of T cell help.

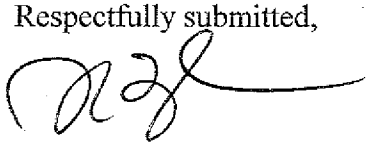
Accordingly, Applicants respectfully submit that WO96/34105 does not teach or suggest administration of a GPI complex which interacts and forms an association with CD1,

resulting in the activation of helper T cells. As such, this reference fails to provide the requisite basis to support an obviousness rejection. Withdrawal of the § 103 rejection based on WO96/34105 is respectfully requested.

***Conclusion***

In view of the foregoing remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Xiaochun Zhu
Registration No. 56,311

Scully, Scott, Murphy & Presser, P.C.
400 Garden City Plaza, Suite 300
Garden City, New York 11530
(516) 742-4343
XZ:ab